REMARKS

I. Status of the Claims

Claims 9, 11-14 and 16-17 are pending in this application, with claims 9 and 13 being independent. Claims 1-8, 12, 15 and 18 were previously canceled. No new claims are added. Amendment to claim 14 is sought to correct a minor typographic error. This amendment does not introduce new matter. All claims have been rejected.

II. Request for withdrawal of finality of the rejection

In the Office Action of August 31, 2006 (hereinafter "the Office Action"), the Examiner has finally rejected all claims in the first Office Action following the filing of a Request for Continued Examination. Applicants respectfully request withdrawal of the finality of the first Office Action. Applicants seek to more fully present all arguments to the Examiner in an effort to gain allowance, or to narrow the issues for presentation on Appeal. Moreover, the Examiner has not considered all cited art. Applicants respectfully request reconsideration of this application in view of the following remarks.

III. Information Disclosure Statement

In the Office Action at page 3, item 7, the Examiner has refused to consider the partial uncertified translation of the document provided. Applicants respectfully believe that the Examiner is obliged to consider at least the partial translation.

Any document submitted in accordance with 37 C.F.R. § 1.98 is to be considered by the Examiner. M.P.E.P. § 609. The Japanese language document and translation provided complies with 37 C.F.R. § 1.98. Applicants are not required to provide certified translations, or complete translations, of foreign-language documents, but only a concise explanation of the relevance as known to Applicants. 37 C.F.R. § 1.98(3). The relevance of the cited Japanese document may be determined by reference to the partial, uncertified translation. Accordingly, Applicants request that the Examiner consider the documents provided in the Information Disclosure Statement of April 28, 2006. If the Examiner considers that a complete translation is necessary, Applicants will obtain a translation and provide it.

IV. The objection to the specification

1. The Examiner's objection

At page 2, item 3 of the Office Action, the Examiner has objected to the specification for alleged incorporation of new subject matter. The objection relies on two inter-related issues:

> Clearly, then the issue is twofold: 1) where specifically in the WO document [WO 92/19759] is the hMP-1 antibody *comprising* the specific V_L and V_H regions (and any other C regions) to be found, and 2) how does this entire genus of antibodies describe the single hMP-1 antibody of the instant specification.

(emphasis in original). Applicants will address, in turn, these two aspects of the objection raised by the Examiner. WO 92/19759 is the Japanese-language publication of PCT application PCT/JP92/00544, which matured as (English language) U.S. Patent No. 5,795,965. To assist in the prompt resolution of this matter, Applicants will refer to sections in U.S. Patent No. 5,795,965 (hereinafter "the '965 patent") rather than the Japanese language WO 92/19759.

2. The '965 patent provides support for a genus of hPM-1 antibodies comprising the specific V_L and V_H regions, and any other C regions.

The specific language sought to be added to the specification is found, *ipsis verbis*, in claim 3 of the '965 patent[1]. A patent is presumed valid and therefore its claims are presumed to be fully described and enabled by the specification. 35 U.S.C. § 282 Therefore, the language sought to be added to the present specification is presumed, as a matter of law, to be fully described and enabled in the '965 patent. Since the '965 patent is based on a translation of WO 92/19759 and has the same specification, WO 92/19759 must also describe and enable the same language sought to be added to the present specification. Accordingly, this aspect of the Examiner's rejection is overcome.

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[1] Including that an hPM-1 antibody *comprises* the specific V_L and V_H regions, and any other C regions.

Even *if* this language was not found in *claim 3* of the '965 patent, the *specification* of the '965 patent provides support for the language sought to be added to the present specification. Applicants have previously identified specific locations, in the documents sought to be incorporated, which provide support. *See, e.g.*, Applicants' June 2, 2004, reply to the May 7, 2004, Advisory Action and January 2, 2004, Office Action in the present application. Specific support for a genus of reshaped (humanized) PM-1 antibodies may be found in the specification of the '965 patent at, for example, col. 3, l. 65 to col. 4, l. 39; col. 6, l. 52 to col. 15, l. 46; col. 21, l. 16 to col. 23, l. 43; col. 25, ll. 46-53; col. 26, ll. 16-47; col. 28, l. 54 to col. 38, l. 4; and col. 46, ll. 58-67.

More generally, it is clear that the '965 patent provides for a genus of reshaped/humanized murine antibodies against IL-6 or IL-6 receptor (IL-6R), methods of making and using them. The '965 patent indicates that antibodies against IL-6 and IL-6R may have therapeutic uses in humans (col. 1, ll. 24-51). However, the currently available murine monoclonal antibodies are highly immunogenic in humans and they therefore have a shortened half-life and increased chance of adverse reactions compared with human antibodies (col. 1, ll. 52-61). Grafting regions responsible for binding to IL-6R from the murine antibody into a human antibody results in "reshaped" antibodies, which have low immunogenicity (col. 2, ll. 10-22). The '965 patent teaches a person of ordinary skill in the art how to make and use reshaped antibodies and specifically applies this technology to PM-1: providing the amino acid sequence of PM-1 antibody and features of reshaped variants.

The sequence of hundreds of human antibodies are known in the art: a search of PubMed identified 2228 protein sequences of human IgG alone. Any one of these human antibodies may be a suitable basis for forming a reshaped, "humanized" PM-1 by swapping murine domains with the corresponding domains from human antibodies. Thus, there are hundreds of possible reshaped or humanized variants of PM-1. Additional amino acid changes can also be introduced by art-known methods. Accordingly, the '965 patent describes and enables hundreds of possible humanized versions of PM-1, and "hPM-1" therefore describes a genus of hundreds of possible antibodies.

In summary, the general teachings; specific portions of the specification; and claim 3 all demonstrate that the '965 patent supports a genus of antibodies which *comprise* specific features. As the '965 patent has the same specification as WO 92/19759, it follows that WO 92/19759 similarly provides for this genus. Accordingly, this aspect of the Examiner's objection has been overcome.

3. The specification is not limited to a single hPM-1 antibody

The second aspect of the objection raised by the Examiner, at page 2, item 3 is:

> 2) how does this entire genus of antibodies [in WO 92/19759] describe the single hMP-1 antibody of the instant specification.

This aspect of the Examiner's objection depends *entirely* on the phrase "[a] preferred example of such a reshaped human antibody is hPM-1" (Specification at pages 10-11), which the Examiner characterizes as limiting to a single reshaped human antibody:

> Note that the instant specification discloses that hMP-1 is *a* (note singular) reshaped human antibody (pages 10-11).

Id. (italics in original). There are two possible interpretations of this aspect of the Examiner's objection. The first is that the Applicants wish to incorporate by reference only a single species of antibody, rather than the genus of antibodies found in WO 92/19759, and that the Examiner is not sure *which* particular species n WO 92/19759 is to be incorporated by reference. Applicants are not seeking to amend the specification to incorporate only a single species of antibody, but seek to incorporate the genus of reshaped hPM-1 provided by WO 92/19759 and the '965 patent. Having clarified this point, Applicants believe that this aspect of the objection is overcome.

The second possible interpretation is that the Examiner regards the sentence spanning pages 10-11 as limiting the scope of that which the Applicants are *entitled* to incorporate by reference. That is, that the use of the singular "a" in this one sentence is a disclaimer of the genus provided by WO 92/19759.

As Japanese does not distinguish between singular and plural forms in same way as English, the original Japanese-language text of the specification at this sentence does not

distinguish between the singular/species and plural/generic forms, and a translation to either singular or plural forms in English is correct. Thus, the relevant sentence could read "Preferred examples of such reshaped human antibodies are hPM-1." As this particular sentence encompasses the plural and generic forms, the Examiner's objection should be withdrawn as it entirely relies on the relevant sentence being limited exclusively to the singular form. If requested by the Examiner, Applicants will provide a statement by a translator and/or amend the relevant sentence in the specification.

Even *if* the specification was originally in English and recited the singular form, this would not be determinative of the issue in support of the Examiner's contention. The specification describes PM-1 as a preferred murine monoclonal (page 6, line 30), and that monoclonal antibodies may be reshaped (page 10). Given that the purpose of reshaping is to remove antigenic regions of murine antibodies by replacing antigenic sections with the corresponding regions from human antibodies, the person of ordinary skill would understand that hundredsr of reshaped version of PM-1 ("humanized" PM-1 or hPM-1) can be generated. Additionally, in reciting to WO 92/195769, the present specification *has* incorporated by reference the entirety of that specification which, as shown above, describes and enables a genus of hPM-1 antibodies. Accordingly, the present specification has already incorporated the genus of hPM-1. To interpret the sentence spanning pages 10-11 as a disclaimer of that which is already part of the specification requires one to afford undue weight to a single sentence and ignore countervailing evidence. The Examiner has not cited any law or provisions of the MPEP that indicate that the language of page 10-11 could function as an effective disclaimer of the genus of humanized PM-1 antibodies, especially given the body of countervailing evidence presented above.

Applicants note that, *even without specific incorporation by reference,* the genus of hPM-1 antibodies described and enabled by WO 92/19759 is already part of the application because knowledge available to those of ordinary skill in the art is *already* part of the application. *See, e.g. Capon v Eshhar* 418 F.3d 1349 (Fed. Cir. 2006); *Falkner v. Inglis* 448 F.3d 1357 (Fed. Cir. 2006); *reh'g en banc den.*, 433 F.3d 1373 (2006); *cert den.* (Dkt No. 06-693, January 22, 2007). Applicants' specific reference to WO 92/19759 merely provides *additional* evidence of the intention to incorporate the disclosure of WO 92/19759 into the

present application. Thus, the genus of hPM-1 antibodies described and enabled by WO 92/19759, and not merely a specific embodiment, are *already* part of the present application.

4. Summary

For at least the above reasons, and further in view of previous arguments of record which are incorporated by reference herein, Applicants respectfully believe that the present objection to the specification is overcome, and request that the Examiner reconsider and withdraw the objection.

V. The rejection under 35 U.S.C. § 112, first paragraph, written description

In the Office Action at pages 2-3, item 5, the Examiner has maintained the rejection of claims 9, 11-14, 16 and 17 under the written description requirement of 35 U.S.C. § 112, first paragraph. The Examiner raised two related issues, which Applicants respectfully traverse.

At pages 2-3, the Examiner has asserted that the disclosure "does not reasonably convey that the inventor(s) had possession of the claimed invention at the time the application was filed." At page 3, second and third full paragraphs, it was asserted that, since the amendment to the specification is allegedly improper, the new claims are also improper and thus comprise the introduction of new matter into the claims; and that only a proper amendment to the specification would allow for withdrawal of the rejection. As Applicants have demonstrated that the amendment sought to be made to the specification *is* proper (Section IV, above), it is believed that the rejection under 35 U.S.C. § 112 is entirely overcome.

Nevertheless, Applicants wish to address, independently of other issues raised by the Examiner, the assertion that the "disclosure does not reasonably convey that the inventor(s) had possession of the claimed invention at the time the application was filed." This statement has two aspects: (a) whether the inventor had possession of the invention and (b) whether the inventor reasonably conveyed this possession.

The question of possession almost always arises where an applicant seeks to patent more than he reasonably can be considered to have invented. The purpose of the written

description requirement is to "ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Reiffin v Microsoft Corp.*, 214 F.3d 1342 (Fed. Cir. 2000). For example, the written description requirement was not met when an applicant was seeking to claim the sequence of human insulin based on the sequence of rat insulin (*Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)); or COX-2 inhibitors based on the development of an assay to identify such inhibitors (*Univ. Rochester v. G.D. Searle & Co.*, 358 F.3d 956 (Fed. Cir. 2004)).

The present application is unlike the situation in case such as *Lilly* or *Rochester,* as it is unchallenged that Applicants were in *actual* possession of the claimed invention. The present application describes the therapeutic use of antibodies against IL-6 and IL-6R and specifically describes the murine monoclonal PM-1. It indicates the desirability of using "reshaped" or "humanized" antibodies in human therapy, and specifically incorporates by reference WO 92/19759, which provides for the genus of reshaped human antibodies against IL-6 and IL-6R, including humanized hPM-1. As WO 92/19759 is knowledge available to those of ordinary skill in the art at the time of filing, and especially as it was specifically referenced in the present specification, Applicants *were* in possession of the presently claimed invention. Not only that, but both WO 92/19759 and WO 96/11020, the corresponding PCT of the present application, are listed on their face as assigned to Chugai Seiyaku Kabushiki Kaisha. Thus, the same entity also has legal possession of any inventions in both applications, at the time of filing, unlike the situation in *Lilly* or *Rochester*. For all these reasons, it is respectfully believed that Applicants had possession of the complete invention as of the time of filing.

The remaining issue, then, is whether Applicants reasonably *conveyed* this possession to the person of ordinary skill in the art. The question of whether the invention is reasonably conveyed usually arises in the context of whether there was actual possession, or if the scope of that which is claimed is commensurate with that "possessed." The Examiner's question, here, appears to be more directed to the adequacy of description *per se*, which is a factual one.

In view of the claims of the '965 patent, a person of ordinary skill in the art is presumed, as a matter of law, to consider that WO 92/19759 describes and enables the genus of hPM-1 antibodies claimed in the '965 patent. In view of the claims of U.S. Patent No. 5,888,510, which matured from the parent of the present application, a person of ordinary skill in the art is presumed, as a matter of law, to consider that the present application has described and enabled a method of treatment comprising the administration of an antibody against IL-6 or IL-6R. The question is then reduced to whether the person of ordinary skill would believe that the present application, directed to methods of treatment with a specific genus of antibodies, has sufficiently incorporated by reference the features of the genus of antibodies provided by WO 92/19759.

As discussed above (*see* IV), the Examiner's refusal to incorporate by reference the disclosure of WO 92/19759 relies on an interpretation of a single sentence that is, at the least, strained and contrary to additional evidence, especially given that the sentence can be translated from the original Japanese to encompass the plural/generic.

Moreover, Applicants' position is supported by the case law. As M.P.E.P. § 2163 notes, possession may be shown in a variety of ways. *See, e.g., Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); R*egents of the University of California v. Eli Lilly,* 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical,* 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The recent case law reiterates that knowledge available to those of ordinary skill in the art, at the time of filing, is already part of the specification.

The most recent case on point is *Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006); *reh'g en banc den.*, 433 F.3d 1373 (2006); *cert den.* (Dkt No. 06-693, January 22, 2007). The Inglis specification described a method of attenuating viruses by inactivating essential genes, and provided examples from herpesvirus. Inglis claimed attenuated poxvirus, but had not provided the essential regions of the poxvirus:

> Falkner argues, *inter alia,* that the Inglis specifications do not adequately describe the poxvirus invention, in light of *Eli Lilly*, because they do not describe the "essential regions" of any

> poxvirus. 119 F.3d 1559. We note, in addition, that Inglis did not attempt to incorporate by reference any literature that described the DNA sequence of the poxvirus genome and the locations of the "essential regions." However, it is the binding precedent of this court that *Eli Lilly* does *not* set forth a *per se* rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art. *See Capon*, 418 F.3d at 1357. . . .
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> Indeed, a requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement.
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> . . . .
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> Indeed, the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification. Accordingly, we hold that where, as in this case accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here "essential genes"), satisfaction of the written description requirement does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences.

(italicized emphasis in original, underlined emphasis added). Thus, even though Inglis had neither described what poxvirus genes were essential, nor incorporated such information by reference, Inglis's claims to attenuated poxvirus complied with the written description requirement because information on what poxvirus genes were essential was readily available in the art. Here, Applicants have specifically referred to WO 92/19759, ensuring that the person of ordinary skill would be in possession of the genus of hPM-1 provided by WO 92/19759, for use in the presently claimed therapeutic methods. Thus, Applicants have not only met, they have *exceeded* the written description requirement as set forth in *Falkner*.

Capon v Eshhar, 418 F.3d 1349 (Fed. Cir. 2006), is also relevant to the present situation. There, the Applicants had described features of chimeric antibodies which were made by combining different regions of antibodies. The Applicants had not provided any specific antibody sequences and were held, by the Board of Patent Appeals and Interferences to have not complied with the written description requirement. The Federal Circuit reversed. Just as with Applicants reference to the genus of hPM-1 in WO 92/19759, providing specific

features, the Federal Circuit in *Capon* found that the parties reference to knowledge available in the art meant that their application contained such knowledge that it complied with the written description requirement:

> The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh. Both parties state that a person experienced in the field of this invention would know that these known DNA segments would retain their DNA sequences when linked by known methods. Both parties explain that their invention is not in discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result.
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> The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. . . . The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.

Id. at 1358. Therefore, in view of both *Falkner* and *Capon*, Applicants have reasonably *conveyed* their possession to the person of ordinary skill in the art, and have therefore complied with the written description requirement of 35 U.S.C. § 112, first paragraph.

For at least these reasons, and in view of remarks previously made of record and incorporated by reference herein, Applicants respectfully believe that the rejection is overcome, and request reconsideration and withdrawal of the present rejection under 35 U.S.C. § 112, first paragraph.

VI. Conclusion

Applicants believe that this application is in condition for allowance, and request favorable reconsideration of it. If the Examiner believes that an interview would further advance the prosecution, he is invited to contact the undersigned attorney by telephone.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extensions under 37 C.F.R. §1.136 and authorize payment of any extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

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